

## ***Hypothyroidism — Treatment Issues: Towards an Indian Consensus***

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### **SUMMARY**

Hypothyroidism was the first endocrine disorder treated by replacement with the deficient hormone, in the form of extracts of animal thyroid glands. Subsequently, the development of purified thyroid hormone preparations and greater understanding of thyroid physiology have made it possible to mimic the function of the normal thyroid gland with thyroid hormone replacement therapy. Thyroid hormone therapy is safe and well tolerated by most patients, and many patients can be treated for prolonged periods with little change in dosage. However, several clinical situations and drugs can alter the absorption, metabolism, and action of exogenous thyroid hormone and therefore may necessitate adjustment of therapy. The range of dose preparations that are available, and the ability of monitor therapy with measurements of serum thyrotropin (TSH) allow the clinician to provide adequate therapy while minimizing both over- and undertreatment.

### **HISTORY OF THYROXINE REPLACEMENT THERAPY**

Thyroid hormone preparations have been used in the treatment of hypothyroidism since 1891, when George Murray injected a phenolic extract of sheep thyroid into a myxedematous patient and achieved the first breakthrough in the management of what until then had been an incurable disease that frequently resulted in a fatal outcome<sup>1</sup>. Shortly thereafter, Murray observed that the beneficial effects of the injected extract could be duplicated by the ingestion of whole sheep thyroid, a finding that subsequently prompted his discovery of the efficacy of a desiccated glycerin extract of thyroid, a

preparation that became the standard agent for hormonal replacement and pituitary TSH suppression. Although synthetic preparations of levothyroxine (L-T<sub>4</sub>) had been widely available since 1958 and synthetic preparations of liothyronine (L-T<sub>3</sub>) had been available since 1956, desiccated thyroid remained the most popular thyroid preparation until the midseventies. The general acceptance of desiccated thyroid rested at least in part on the assumption that the combination of L-T<sub>4</sub> and L-T<sub>3</sub> in desiccated thyroid offered a distinctive clinical advantage over the exclusive use of either one or the other of the synthesized hormonal constituents. This line of reasoning held sway until the general recognition that: 1) T<sub>4</sub> is converted to T<sub>3</sub> peripherally;<sup>2</sup> 2) about 80% of extrathyroidal T<sub>3</sub> originates from the tissue conversion of T<sub>4</sub>;<sup>3</sup> and 3) T<sub>4</sub> serves largely as a prohormone for T<sub>3</sub>, an iodothyronine that is much more strongly bound to thyroid hormone receptor than is T<sub>4</sub>.<sup>4</sup>

These findings favored the use of L-T<sub>4</sub> in the treatment of hypothyroidism. Thus, the levels of serum T<sub>4</sub> and T<sub>3</sub> are relatively constant after oral administration, given the relative long 6-day half-life of T<sub>4</sub>, and the comparatively short 1-day half-life of T<sub>3</sub>.<sup>5</sup> Stable serum levels of these hormones facilitates titration of the L-T<sub>4</sub> dose to achieve preassigned ranges of thyroid hormones. Two independently initiated studies showing the usefulness of L-T<sub>4</sub> in thyroid hormone replacement followed, one published in 1973<sup>5</sup> and the other in 1974<sup>6</sup>. In both studies the criterion for establishment of the euthyroid status was normalization of TSH in response to TRH administration. Both studies showed that the replacement dose was substantially less than the 200-400 mcg/day range recommended in the package insert of L-T<sub>4</sub> preparations and in the major textbooks of medicine of the time. One study found that the average replacement

dose was 127 mcg/day,<sup>5</sup> whereas the other found an average value of 169 mcg.<sup>6</sup> The fact that the high dosage range for L-T<sub>4</sub> administration had been accepted for so many years emphasized the principle that even a doubling in dosage delivery to a hypothyroid patient may not cause clinically obvious symptoms. The demonstration that the daily dose of L-T<sub>4</sub> could be conveniently monitored and titrated served to popularize the use of this agent in the management of hypothyroidism. L-T<sub>4</sub> is now virtually universally used.

Introduction of second and third generation TSH assays obviated the use of TRH testing to determine the level of TSH in a given patient receiving replacement treatment<sup>7</sup>. However, the use of the very sensitive third generation assay that allows the measurement of subnormal TSH concentrations has raised a set of new issues that will be considered below.

### PHARMACOLOGY OF THYROID HORMONE PREPARATIONS

Several preparations of thyroid hormone are available for treatment of patients with hypothyroidism; in India and USA they are levothyroxine (T<sub>4</sub>), liothyronine (triiodothyronine, T<sub>3</sub>), liotrix (a 1:4 combination of T<sub>3</sub> and T<sub>4</sub>), and thyroid USP (dissicated animal thyroid containing T<sub>3</sub> and T<sub>4</sub> in the form of thyroglobulin). The latter and other thyroid extract preparations were used until synthetic preparations of T<sub>4</sub>, T<sub>3</sub>, and T<sub>4</sub> plus T<sub>3</sub> were introduced. Subsequent studies in humans and animals revealed that about 80% of serum T<sub>3</sub> is produced in peripheral tissues by deiodination of T<sub>4</sub>, that administration of T<sub>3</sub> is followed by marked fluctuations in serum T<sub>3</sub> concentrations, and that administration of T<sub>4</sub> alone results in adequate serum and tissue concentrations of T<sub>4</sub> and T<sub>3</sub> and replicates normal thyroid physiology. Now the only recommended and available thyroxine in India is L-T<sub>4</sub> (Thyronorm, Eltroxin).

The most widely used and the preferred preparation for treatment of hypothyroidism is T<sub>4</sub>. Overall, about 70-80% of an oral dose is absorbed, mostly in the proximal small bowel; in contrast, almost 100% of an oral dose of T<sub>3</sub> is absorbed. The advantages of T<sub>4</sub> include its long half-life (~7 days), reliable absorption, small (<15%) fluctuation in serum T<sub>4</sub> concentrations between single daily doses, ease of dose titration based on multiple available tablet strengths, and ease of measurements of its serum concentration. Although the proportion of hypothyroid patients receiving T<sub>4</sub> has increased steadily, even today many are probable still being treated with thyroid cancer extract or a combination of T<sub>4</sub> and T<sub>3</sub>.

### BRANDS AND BIOAVAILABILITY

The T<sub>4</sub> content of tablets is standardized by high pressure liquid chromatography and must be between 90% and 110% of the stated amount. Before 1982, the standard was based on iodine content, and therefore included not only authentic T<sub>4</sub> but also biologically inactive degradation products and, in thyroid extracts, mono- and diiodotyrosines. Several brand-name and generic preparations are available, and their bioavailability is similar. T<sub>4</sub> tablets seem to be stable, but may lose potency if exposed to moisture, light, or air. Although a well-standardised product, reduced T<sub>4</sub> content was reported in tablets from one manufacturer, resulting in high serum TSH concentration among hypothyroid patients receiving supposedly adequate replacement in a defined geographic region. Tablets available now in India range in size from 25-300 µg, which allows very precise replacement in nearly all patients. However bio-equivalence data of Indian preparation find only two thyroxine brands (Thyronorm and Eltroxin) meet the set standards.

There are several drawbacks to administration of T<sub>3</sub> and T<sub>3</sub>-containing preparations, in comparison with administration of T<sub>4</sub>. T<sub>3</sub> is rapidly absorbed, with peak T<sub>3</sub> concentrations being reached 2-4 hours after oral administration; doses of as little as 25 µg result in supranormal serum T<sub>3</sub> concentrations for 6-8 hours. As compared with T<sub>4</sub>, the circulating half-life is much shorter (approximately 1 day). As a result of these characteristics of T<sub>3</sub>, absorption and metabolism, serum T<sub>3</sub> concentrations vary in the hours after dosing, as noted above.

### T<sub>3</sub>/T<sub>4</sub> Controversy

Despite the standard of only supplementing with levothyroxine (T<sub>4</sub>) for thyroid replacement, there is some preliminary evidence to show some patients feel better when given both levothyroxine (T<sub>4</sub>) and triiodothyronine (T<sub>3</sub>). Thyroid extracts are generally not recommended due to variation in potency and contains large amounts of T<sub>3</sub> which can cause palpitations and tremors. Obviously, with only one small human study quoted, there is not enough evidence to support this recommendation. Although T<sub>4</sub> is the recommended form of thyroid hormone replacement in hypothyroidism, the use of combined T<sub>4</sub> and T<sub>3</sub> treatment is again being considered. In thyroidectomized rats, T<sub>4</sub> treatment alone does not normalize T<sub>3</sub> concentrations in all tissues, whereas combined T<sub>4</sub> and T<sub>3</sub> treatment dose. In a study of hypothyroid patients receiving T<sub>4</sub> in whom 12.5 µg T<sub>3</sub> was substituted for 50 µg T<sub>4</sub>, the combination resulted in

improvement on several scales of cognitive performance and mood compared with  $T_4$  treatment alone, whereas serum TSH concentrations were similar during both treatments. However, the ratio of  $T_3$  to  $T_4$  during combination treatment in this study was considerably lower (mean 1:10) than that in the commercially available preparation of  $T_4$  and  $T_3$  or in thyroid extract. Also there is some evidence to show that  $T_3$  may have some effect on cognitive function on the elderly which prompted publication of a few scant studies. One need to re-think your stance on  $T_3$  treatment for thyroid disease but should be pushing more for  $T_3$  studies. What I mean is pushing for  $T_3$  studies for the right reason, which is because  $T_3$  can help alleviate the misery many patients naturally because it is so potent the administration of this hormone has to be very precise. *Currently except L- $T_4$  no other form including  $T_3$  or extracts is recommended.*

#### **Therapeutic Approach to Hypothyroidism: Goals and Monitoring**

The goal of treatment of hypothyroidism is to normalize thyroid status in peripheral tissues, whatever the cause of the hypothyroidism. The usual approach is to give sufficient  $T_4$  to ameliorate all symptoms of hypothyroidism and, in patients with primary hypothyroidism, to reduce serum TSH concentrations to within the normal range; doses effective in these regards raise serum total and free  $T_4$  concentrations to well within their respective normal ranges or just above them, and serum total and free  $T_3$  concentrations to within the normal range (the difference representing the thyroidal contribution to serum  $T_3$  concentrations in normal subjects). Measuring effects of  $T_4$  on tissues other than the pituitary gland accurately is very difficult, and no other measurement is as sensitive to small changes in dose of  $T_4$  as is that of serum TSH. Thus, measurements of serum TSH are the best way to identify patients who are receiving too much  $T_4$  (low serum TSH concentration) and those who are receiving too little (high serum TSH concentration). In most hypothyroid patients treated with  $T_4$  there is a close correlation between serum free  $T_4$  concentration and measurements of resting energy expenditure and other thyroid hormone actions, notwithstanding the insensitivity of these latter measurements. Rare patients, however, have been reported in whom there was a disparity between serum TSH concentrations and clinical measurements of thyroid hormone action at the tissue level, such as serum cholesterol and ankle reflex relaxation time. The serum TSH value is not an accurate reflection of thyroid status in patients with central hypothyroidism. In these

patients some estimate of serum free  $T_4$  should be used as the indicator of thyroid status and to monitor the efficacy of treatment. A similar approach should be used in patients recently treated for thyrotoxicosis, in whom serum TSH concentrations may remain low for several months due to the slow recovery of TSH secretion from prolonged suppression while the patient was thyrotoxic.

#### **Should the TSH be the Sole Laboratory Criterion of Thyroid Status?**

Clearly, TSH cannot be used as a sole criterion of thyroidal status in patients with central hypothyroidism (pituitary or hypothalamic), given the fact that the TSH level in such patients can be very low, normal, or even slightly elevated<sup>8</sup>. The coexistence of normal or marginally elevated TSH and low levels of serum free  $T_4$  may be due to altered glycosylation patterns of TSH resulting in a lowered ratio of the biological potency immunoreactivity<sup>9</sup>. Thus, for patients with central hypothyroidism, the levels of free  $T_4$  or the free  $T_4$  index should serve as the primary laboratory parameter for determining the L- $T_4$  replacement dose. As approximately 20% of extrathyroidal  $T_3$  results from direct thyroidal secretion, the level of circulating  $T_4$  should be in the upper half of the normal range. Although the finding of a serum  $T_3$  concentration in the midnormal range can be useful as further confirmation of the euthyroid status of the patient, a low  $T_3$  concentration can also be a reflection of associated nonthyroidal disease. Even in patients with primary thyroidal failure, the serum  $T_4$  concentration provides useful corroboration of the clinical state. A lowering of serum  $T_4$  accompanied by a rise in TSH confirm the need for increasing the L- $T_4$  dose. This combination of changes can also be due to a further decrease in residual thyroidal secretion of  $T_4$  or to noncompliance by the patient or switching L- $T_4$  preparations from one brand to another. Rarely, an elevation of a TSH assay is an artifact created by circulating mouse heterophile antibody<sup>10</sup>. Lastly, a small minority of patients with catabolic nonthyroidal disease<sup>11</sup> may exhibit TSH values below the lower limits of the normal range (0.4-5.0 mU/L) without any ancillary data, suggesting either clinical hypothyroidism or hyperthyroidism. Similarly, both dopamine infusion<sup>12</sup> and glucocorticoid administration<sup>13</sup> may lower the serum TSH level without overt clinical evidence of thyroid dysfunction. These considerations emphasize the usefulness of the serum  $T_4$  or Free  $T_4$  level or the free  $T_4$  index in assessing the thyroid status of patients suspected of being hypothyroid and in following hypothyroid patients who are being replaced with L- $T_4$ .

### Initiation of Therapy

The initial dose of  $T_4$  should be based on the age of the patient, the severity and duration of hypothyroidism, and the presence of any other associated disorders. Healthy patients under the age of 60 years with no history of cardiac or respiratory disease can be started on a full replacement dose of  $T_4$ , which is about 1.6-1.8  $\mu\text{g}/\text{kg}$  body weight/day (usually 75-125  $\mu\text{g}/\text{day}$  in women and 125-200  $\mu\text{g}/\text{day}$  in men), given once daily. These doses must be given for 4-8 weeks before their tissue effects and serum  $T_4$  and TSH concentrations reach a steady state. In general, bioavailability is not known to be affected by food, but is prudent to advise the patient to take their daily dose of  $T_4$  at the same time in relation to eating everyday.

Older patients (>60 years) required 20-30% less  $T_4$  per kg ideal body weight than do younger patients. Because of the very small risk of inducing angina or a cardiac arrhythmia, it is prudent to treat even healthy older patients initially with 50  $\mu\text{g}/\text{day}$ , increasing the dose by 25  $\mu\text{g}$  at intervals of at least 6 weeks.

The underlying cause of thyroid disease also can influence the dose requirement. For example, patients with primary hypothyroidism caused by chronic autoimmune thyroiditis or total thyroidectomy require slightly higher doses of  $T_4$  than do patients with Graves' hyperthyroidism made hypothyroid by radioactive iodine or surgical therapy, because the latter are more likely to have some remaining autonomously functioning thyroid tissue.

Hypothyroid patients who are unable to take oral medication for a brief period of time (several days) do not need parenteral therapy, owing to the long half-life of  $T_4$ . For those patients who cannot be given  $T_4$  orally for prolonged periods, or who are unable to absorb  $T_4$ , it can be given intravenously. The daily intravenous dose should be 70-80% of the usual oral dose, based on the fraction of an oral dose that is absorbed.

### Thyroxine Therapy in Patients with Underlying Cardiac Disease

In hypothyroid patients,  $T_4$  can improve cardiac performance by reducing systemic vascular resistance, reducing end-diastolic volume, increasing the strength of contraction, and increasing cardiac output. Nonetheless, there has been concern that administration of  $T_4$  to hypothyroid patients with ischemic or other cardiac disease would have adverse cardiovascular effects. There is, however, little evidence to support this concern. For example, among a large group of

hypothyroid patients treated with thyroid hormone, only 2% developed new-onset angina pectoris. Among those patients with preexisting angina, 38% improved, 46% had no change, and only 16% worsened.

Despite the low risk, given the serious consequences of worsening ischemic heart disease, patients with cardiac disease or risk factors for it should be given  $T_4$  cautiously, for example 25  $\mu\text{g}/\text{day}$ . If cardiac disease is present or suspected, evaluation and treatment can proceed as would otherwise occur. For example, patients with angina and hypothyroidism should in most instances have appropriate evaluation and treatment for coronary artery disease at the same time as  $T_4$  therapy is initiated.

### Monitoring Thyroxine Therapy

The intensity with which  $T_4$  therapy is monitored depends on the severity of hypothyroidism and the clinical context. Those patients given low doses because of age or another illness should be reevaluated in 6 weeks, and the dose increased in small increments. For those patients initially given what is estimated to be full replacement dose, the patient should be reevaluated and serum TSH should be measured in about 8 weeks. The dose of  $T_4$  should be increased if the serum TSH concentration is still high, or decreased if it is low. Dose changes of 25  $\mu\text{g}$  are usually sufficient when making an adjustment, depending on the deviation of serum TSH from normal. If the dose is not changed, the patient should be reevaluated and serum TSH measured again in 4-6 months, because that clearance of  $T_4$  can be increased after the euthyroid state is established. If, as a consequence of the change in dose, the serum TSH concentration becomes abnormal at the other extreme, tablets are available that are 12- $\mu\text{g}$  increments between the commonly used doses of 75, 100, 125 and 150  $\mu\text{g}$ .

Once the appropriate dose of  $T_4$  is determined, annual reevaluation and measurements of serum TSH are recommended. Most patients can be treated with the same dose until the seventh to eighth decade of life, when the dose may need to be decreased. The requirement for  $T_4$  can be altered by several conditions and medications.

The relationship between serum TSH and  $T_4$  concentrations is log-linear, so that a small reduction in serum  $T_4$  concentration results in a large increase in serum TSH concentrations, as demonstrated in a study of patients receiving a stable dose of  $T_4$  who had normal serum TSH concentrations in whom the dose then was increased or decreased in increments of 25  $\mu\text{g}/\text{day}$ . These results explain why very small changes in  $T_4$  dose can result in substantial changes in serum TSH concentrations.

### Treatment of Central Hypothyroidism

Patients with central (secondary) hypothyroidism also should be treated with  $T_4$ , but, as noted earlier, serum TSH measurements are not useful for monitoring therapy. Instead, measurements of serum free  $T_4$  (direct or indirect) should be used, although measurements of serum total  $T_4$  may be adequate if the patient is known to have normal serum binding of  $T_4$ . The goal of treatment should be a serum  $T_4$  concentration in the middle or upper end of the normal range for the test used. It is important that other aspects of pituitary function be assessed, especially pituitary-adrenal function. Patients with both hypothyroidism and hypocortisolism may have only symptoms of hypothyroidism, but then develop symptoms of hypocortisolism when  $T_4$  therapy is begun, because the metabolic clearance of cortisol is reduced in hypothyroidism. For this reason, if there is any question of the adequacy of adrenal reserve, in both  $T_4$  and hydrocortisone should be given until hypothalamic-pituitary-adrenal function can be evaluated.

### Response to Thyroxine Treatment

The response to  $T_4$  therapy should be assessed both clinically and biochemically. Normalization of clinical and biochemical manifestations of hypothyroidism, however, occurs at different times and can vary among patients. The earliest change usually is normalization of the serum  $T_4$  concentration, which occurs after several weeks of treatment. Normalization of the serum TSH concentration may require up to 8 weeks, depending on the magnitude of the initial elevation. Most patients note improvement of symptoms in several weeks, but complete recovery usually requires several months. A substantial fraction of patients with hypothyroidism complain of weight gain and have an expectation of weight loss when they are treated. Most of the weight that is lost after treatment is begun, however, is fluid, so that the decrease in weight does not usually exceed 10% of body weight, and the weight that is lost usually regained in the following months.

### Conditions Associated with Altered Thyroxine Requirements

Several conditions and drugs can alter the requirement for  $T_4$  (Table 1). Older patients, especially those in their sixties or seventies, may need less  $T_4$ , perhaps due to a decrease in  $T_4$  clearance. Hypothyroid patients receiving  $T_4$  replacement who are treated with an androgen also need less  $T_4$ , due to a reduction in the  $T_4$  pool as a result of a decrease in serum thyroxine-

binding globulin (and loss of ability to reduce  $T_4$  secretion to compensate or the decrease in binding).

**Table 1:** Circumstances associated with altered  $T_4$  requirements

Reduced requirement
Older patients
Androgen therapy
Increased requirement
Pregnancy
Malabsorption
Mucosal disease (e.g. sprue)
Short bowel (e.g. postjejunoileal bypass)
Drugs or dietary supplements
Reduced absorption
High-fiber diet
Sucralfate
Aluminum hydroxide
Ferrous sulfate
Cholestyramine
Sodium polystyrene sulfonate (Kayexalate) <sup>a</sup>
Calcium carbonate <sup>a</sup>
Increased clearance
Rifampin
Carbamazepine
Phenytoin
Reduced $T_4$ to $T_3$ conversion
Amiodarone
Selenium deficiency
Mechanism unknown
Lovastatin <sup>a</sup>
Sertraline

<sup>a</sup> Single case or very small number of cases

More often, an increase in the dose of  $T_4$  is needed. Most hypothyroid women require an increase in  $T_4$  dose during pregnancy. The magnitude of the increase averages 50%, but it is variable and is related to the amount of residual thyroid tissue. It is due at least in part to the increase in serum thyroxine-binding globulin that occurs during that first 15-20 weeks of pregnancy. The prepregnancy dose of  $T_4$  can be resumed after delivery.

Patients who undergo bowel resection, have intestinal disease, or eat a lot of fiber may malabsorb  $T_4$ , and hence need a large dose. Similarly, several drugs may cause malabsorption of  $T_4$ , including sucralfate, aluminum hydroxide, ferrous sulfate, cholestyramine, and possibly sodium polystyrene sulfonate and calcium

carbonate. Other drugs that can lead to need for more T<sub>4</sub> are rifampin, carbamazepine, and phenytoin, which increase T<sub>4</sub> clearance and amiodarone, which slows T<sub>4</sub> clearance, inhibits T<sub>4</sub> to T<sub>3</sub> conversion, and may antagonize the peripheral action of T<sub>3</sub>. Other drugs reported to increase the need for T<sub>4</sub> are lovastatin and sertraline. Many of these interactions have been described in only a few patients, and only rarely was the interaction confirmed in the same patient. For the drugs that decrease T<sub>4</sub> absorption, separation of the times at which the T<sub>4</sub> and the drug are taken by several hours eliminates the effect.

### Adverse Effects of Thyroxine Therapy

Excessive T<sub>4</sub> treatment causes subclinical or overt thyrotoxicosis. Patients with subclinical thyrotoxicosis have few if any symptoms of thyrotoxicosis, but may be at risk for excess bone loss and cardiac arrhythmias or cardiac dysfunction. Excess bone loss may occur in postmenopausal women who receive sufficient T<sub>4</sub> to reduce TSH secretion below normal, and patients who have low serum TSH concentrations may have increased pulse rates and increased cardiac wall thickness and contractility, as well as an increased risk of atrial fibrillation. Hair fall and sometimes even alopecia is often a common occurrence which may respond to adjuvant vitamin E preparations.

## TREATMENT FAILURES

### Persistently High Serum TSH Concentrations

In some patients serum TSH concentrations remain high despite a T<sub>4</sub> dose that should be adequate. Poor compliance is the most common reason for this finding and it should be suspected in patients receiving excessive doses of T<sub>4</sub> for their size or in those with widely varying thyroid function studies while taking the same prescribed dose. In patients who take multiple daily doses just before a follow-up visit, serum TSH concentrations may be high despite the presence of normal or even high serum T<sub>4</sub> concentrations.

A persistent elevation in serum TSH despite good compliance may be the result of one of the conditions or drugs that increases the need for T<sub>4</sub> listed in Table 1. In their absence, changing the brand of T<sub>4</sub> can result in improved absorption. Despite the identical content of T<sub>4</sub> in different brands, there is enough variation in the dissolution times among them that absorption of some brands may be decreased in patients with rapid intestinal transit. Finally, a very small number of patients have persistently high serum TSH and T<sub>4</sub> concentrations.

These patients should be evaluated for resistance to the action of thyroid hormone, particularly if they have undergone thyroidectomy or received radioactive iodine therapy for a mistaken diagnosis of hyperthyroidism in the past.

### Hypothyroid Symptoms Despite Normal Thyroid Function Study Results

Hypothyroid patients may complain of persistent symptoms despite adequate T<sub>4</sub> therapy. This is especially true of those previously given excessive doses of T<sub>4</sub>. Given the potential complications of excessive doses, it is important to educate the patient to the fact that a normal serum TSH concentration is the best goal of T<sub>4</sub> treatment. Because T<sub>4</sub> has such varied effects, it is not unusual for patients to attribute a broad range of symptom to inadequate therapy, and some will change their dose of T<sub>4</sub> based on their symptoms. Because of the long half-life of T<sub>4</sub> and the unreliability of the subjective assessment of thyroid hormone-related symptoms, this practice is ineffective and even dangerous, and should be discouraged. Many patients are responsive to education about thyroid hormone testing and monitoring of therapy, along with reassurance. If symptoms persist, other causes for them should be investigated.

### How Tightly Should Hypothyroid Patients be Regulated with L-T<sub>4</sub>?

The third generation TSH assay is becoming increasingly popular by virtue of its high sensitivity and its ability to set upper assay limits (< 0.05 mU/L) for patients with clinical hyperthyroidism. By the same token, this test may present a difficult dilemma when the dose of L-T<sub>4</sub> taken by a hypothyroid patient results in a serum concentration of TSH in the gray zone that lies below the lower limit of normal (0.5 mU/L) but above the upper bounds set for clinical hyperthyroidism (0.05 mU/L). Under such circumstances, the serum free T<sub>4</sub> and free T<sub>3</sub> indexes may still be within the normal population range. The association of such normal levels of free T<sub>3</sub> or free T<sub>4</sub> with depressed concentrations of TSH can be explained if one assumes that the set-point for feedback TSH control is determined for each individual in very narrow bounds of serum free T<sub>3</sub>, much narrower than the range in the normal population. For example, if the set-point for T<sub>3</sub> in a given patient maintained on L-T<sub>4</sub> **replacement therapy** is 100 ng/dL, an increment of 10 ng/dL during the course of treatment may reduce the pituitary TSH feedback system to subnormal levels even though the new steady state value

of 110 ng/dL  $T_3$  is well below 160 ng/dL, which is widely accepted as the upper limit of serum  $T_3$  in the normal population. Such a patient probably would exhibit a gray zone TSH (between 0.05-0.5 mU/L). Although biochemically hyperthyroid, the patient would not be expected to manifest any obvious clinical symptoms. A similar argument could be made for an increase in TSH as a result of a small decline in serum  $T_3$  and  $T_4$  but within the normal population range. The practical problem facing the practicing physician is to determine whether such small excursions of TSH concentrations outside the normal range warrant further adjustment of the daily dose. It has been noted that such discrepancies are relatively common not only during the initial stages of L- $T_4$  replacement but also during yearly follow-up visits. Concern for such deviations in TSH value is justified only if two conditions are met: 1) that the deviations in TSH value observed are truly indicative of the average TSH maintained over many months and 2) that the steady state changes in the range observed are, in fact, associated with long term health risks. Unfortunately, neither of these questions can be answered in a definitive fashion at this time. With regard to the first point, Fish, et al<sup>14</sup> observed considerable variation in TSH levels when serial determinations were made with a second generation assay in five hypothyroid patients maintained on constant L- $T_4$  **replacement therapy**. If the levels of TSH are only slightly elevated or depressed by third generation assays, repeat TSH may be helpful before changing the dose. As approximately 6-8 weeks are required for  $T_4$  and  $T_3$  levels to achieve a new steady state, repeat determinations should be postponed for an additional 2 months after a change in dose. Tight replacement schedules make sense only if the second assumption is also fulfilled: namely that TSH deviations from the normal range result in potentially serious health problems. Two potential target organs that are currently under suspicion are the skeletal system and heart. Several series that have evaluated the effects of L- $T_4$  replacement on bone mineral density are currently available.<sup>15,16</sup> Most but not all of such studies conclude that excessive thyroid hormone **replacement therapy** results in decreased bone mineral density. However, there is disagreement with respect to the areas and age groups most affected. There is also a divergence of opinion as to whether the decrease in bone mineral density induced by L- $T_4$  replacement actually results in an increased fracture rate<sup>17,18</sup>. In essence, it appears unlikely that minimal overreplacement should have serious repercussions with respect to either bone mineral density or fracture rate. Recently, claims have been made that patients with thyroid cancer maintained on long

term TSH suppression therapy exhibit increased heart rate, increased prevalence of cardiac arrhythmias, enhanced left ventricular systolic function, and increased left ventricular mass<sup>19</sup>. Concomitant treatment with cardioselective adrenergic blocking agents antagonized the effects of thyroid hormone<sup>20</sup>. However, the TSH assay used by these researchers did not allow them to distinguish between suppression into the gray zone subclinical range and the clinically apparent TSH range. As many of their patients manifested symptoms, it appears likely that such individuals would have had TSH levels below 0.05 mU/L had third generation TSH assays been used. Of interest is the recent report of an increased incidence of ischemic heart disease in patients under the age of 65 yr receiving L- $T_4$  therapy<sup>21</sup>. However, no difference in incidence was observed between those who exhibited TSH suppression and those who did not. Similarly, gray zone elevations of TSH in subclinical hypothyroidism may have an effect on lipid patterns and predisposed to atherogenesis. However, these effects do not appear to be marked, and in some patients, restoration of TSH levels after the administration of L- $T_4$  failed to normalize the lipid patterns<sup>22</sup>.

### Practice Points

Thus, it appears prudent to make reasonable efforts to normalize the serum TSH level in hypothyroid patients undergoing **replacement therapy** with L- $T_4$ . Keeping the TSH concentration rigidly in the 0.4-4.0 mU/mol-L range would be expensive, require multiple blood samplings, and most likely not contribute significantly to the health of the patient. The third generation TSH assay is the best and must be used-After an initial equilibration during which L- $T_4$  doses are changed at 2-month intervals, patients are seen, in general, at yearly intervals. However, patients are advised to be rechecked when they become pregnant or require medications known to interfere with the absorption or metabolism of L- $T_4$ . Careful distinctions should be made between efforts to replace thyroid hormone in hypothyroid patients and efforts to suppress the production of the last vestige of TSH in the treatment of patients with benign or malignant growths. Ideally, in the case of **replacement therapy** one would like to achieve a TSH concentration within the normal range. With suppression, one might wish to maximally reduce the level of circulating TSH to arrest the growth/goitrogenic process. In the case of thyroid cancer, one might even be willing to accept potentially adverse consequences of supraphysiological doses of L- $T_4$ . In such suppressive doses, analysis of the relationship

between TSH and thyroglobulin levels showed that thyroid hormone treatment was effective in reducing the level of serum thyroglobulin only when the level of TSH was initially elevated above the normal range. Doses of L-T<sub>4</sub> that lowered the level of TSH below the normal TSH range had no additional effect. It is prudent to maintain the level of TSH in patients with thyroid cancer in the range of 0.1-0.4 mU/L. Clearly, additional studies are necessary to test the assumptions underlying these recommendations. Similarly, the efficacy of suppressive doses of L-T<sub>4</sub> in the management of patients with thyroid nodules has been challenged in three prospective randomized studies<sup>24-26</sup>. In contrast, a prospective randomized placebo-controlled study has shown that a suppressive dose of L-T<sub>4</sub> slows the growth of multinodular goiter. It is not clear, however, whether beneficial effects in this study were due to the lowering of initially supranormal levels of serum TSH. These findings also raise questions concerning whether efforts to reduce TSH levels to below the euthyroid range are warranted in the management of benign processes. Succinct Indian reviews and original work of the author available for further reading<sup>28,35</sup>.

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